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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/300,959	04/27/99	ZANETTI M	P-ZA-3519

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EXAMINER	
BECKERLEG,A	
ART UNIT	**PAPER NUMBER**
1632	14

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/300,959	Applicant(s) ZANETTI, MAURIZIO	
	Examiner Anne M Beckerleg	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above claim(s) *1,2,5-17,22-28 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-4,18-21,29-32 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment received on 4/30/01 has been entered. Claim 34 has been added. Claims 1-34 are pending in the instant application. Claims 1-2, 5-17, 22-28 and 33 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8. Claims 3-4 18-21 and 29-32 are active in the instant application. An action on the merits follows. Please note that the examiner of record has changed for this application, see page 11.

Those sections of Title 35, US code, not included in this action, can be found in the previous office action, paper no. 10.

Priority

The applicant argues that the provisional application 60/083,154 substantially describes the instant invention as claimed and provides sufficient description to enable the practice of the instant methods. The enablement of the instant specification, and its parent, the 60/083,154 application is addressed in detail below in the rejection of the claims under 35 U.S.C. 112, first paragraph. However, in regards to priority, the examiner acknowledges support in the provisional application for claims 3-4, 18-19, and 29-31. The provisional application, which is a photocopy of

the applicant's 1997 DNA and Cell Biology paper, does not disclose nucleic acids comprising a polypeptide fused with a cytokine, or the targeting a nucleic acid to hematopoietic cells *ex vivo* as part of a method for treating a condition. The applicant's arguments do not address these limitations. Therefore, claims 20-21 and 32 are not granted the priority date of the provisional application, and are granted the priority date of the instant application, April 27, 1999. The applicant is, however, invited to point out where in the specification of the provisional application support for these limitations can be found.

Claim Rejections - 35 USC § 112

The rejection of claims 3-4, 18-21, 29-32, and 34 under 35 U.S.C. 112, first paragraph, is maintained in part. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

In view of applicant's arguments the scope of enablement has been modified as follows: the specification is enabling for methods of stimulating an immune response *in vivo* by intrasplenic injection of a plasmid DNA encoding an antigen operatively linked to the immunoglobulin heavy chain enhancer and methods of treating *Plasmodium falciparum* malaria sporozoites in a mammal by intrasplenic injection of γ1NANP/GM-CSF. Applicant's arguments regarding the previous limitation to treatment of mice is therefore moot.

The applicant argues that the methods of treating *Plasmodium falciparum* can be practiced without boosting with the γ1NANP/GM-CSF plasmid based on the specification's report that primary immunization leads to immune responses. As noted above, the specification is found to be enabling for methods of treating *Plasmodium falciparum* malaria sporozoites in a mammal by intrasplenic injection of γ1NANP/GM-CSF. However, as discussed in detail in the previous office action, the specification is not enabling for the treatment of *Plasmodium falciparum* malaria sporozoites by intrasplenic injection of γ1NANP in the absence of GM-CSF. While the γ1NANP plasmid generated antibody responses following intrasplenic injection, these antibodies have not been correlated with any treatment effect. Further, the specification on page 109 states that the immunization with γ1NANP/GM-CSF generated four fold high levels of IgG1 anti-NANP than γ1NANP alone, and that the increased antibody titer observed with γ1NANP/GM-CSF was determined to be immunologically relevant. Thus, in the absence of GM-CSF, the IgG1 antibody titer generated by γ1NANP alone does not appear to be immunologically relevant. Further, as discussed in detail in the previous office action, the specification does not provide sufficient guidance as to the level of expression of any and all genes expressed using the instant methods that correlates with the treatment of any and all conditions in any mammal, or provided guidance as to the other cytokines other than GM-CSF that can be used in increase immune responses. It is noted that the applicant's working examples disclose that γ1NANP/IL-2

does not increase antibody titers compared to γ1NANP alone. The applicant has not addressed these issues.

While claims 3-4, 18-21, and 34 have been limited to B cell specific expression elements, claims 29-32 continue to recite the broader limitation of hematopoietic cell expression elements. The applicant argues that the specification provides sufficient guidance for hematopoietic cell expression elements other than the immunoglobulin heavy chain enhancer/promoter. The applicant further states that hematopoietic cell specific promoters are known in the art. The specification, as discussed in the previous office action, fails to teach any promoter element other than the immunoglobulin heavy chain promoter/enhancer. Page 28, cited by the applicant, simply cites that hematopoietic cell expression elements can be used in the instant invention without providing a single example of any such promoter. Pages 63-69 discuss vectors which encode the immunoglobulin heavy chain promoter/enhancer. Further, the claims are directed towards methods of treating disease by generating an immune response. The specification fails to provide any evidence that any "hematopoietic cell expression element" is capable of expressing sufficient levels of any antigen to generate a therapeutic immune response against any disease or condition in any mammal. At the time of filing, the expression of therapeutic levels of a gene in target cells using any of the currently available vectors was considered highly unpredictable. In particular, Verma et al. cites an example of an *ex vivo* gene therapy attempt where a retrovirus was used to express factor IX in fibroblasts which were then grafted into an immunocompromised murine host. According to Verma, " within five to seven days of transplanting the infected cells back into

mice, expression of factor IX is shut off", and that appropriate enhancer-promoter combinations are necessary to override the 'off switch'. Verma concludes by stating that, "the search for such combinations is a case of trail and error for a given cell type" (Verma, (1997) Nature, 389, page 240). Thus, in view of the art recognized unpredictability of promoter selection such that therapeutic levels of gene expression are achieved in target cells *in vivo,* the statement that hematopoietic cell specific promoters have been taught in the art is insufficient to overcome the lack of guidance provided by the specification. The applicant is further reminded that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). Also, 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. In re Fisher, 166 USPQ 18, 24 (CCPA 1970). Thus, in view of the unpredictability of expressing therapeutic levels of gene expression in any vector using any promoter element, the lack of guidance and/or working examples provided by the specification for any hematopoietic cell promoter other than the immunoglobulin heavy chain promoter/enhancer, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

In regards to routes of immunization other than intrasplenic, the applicant argues that the specification identifies other target tissues, such as lymph nodes. However, as previously noted, the cellular composition of the spleen versus gut associated lymph organs, or lymph nodes is very

different in terms of the percentages of different antigen presenting cells and the types of antigen presenting cells present. While the specification demonstrates that direct injection of the spleen results in the generation of immune responses, the specification fails to provide any evidence that the administration of the nucleic acids to any other lymphoid tissue would result in comparable levels of antibody or T cell mediated responses. Further, while claims 3-4, 18-21, and 34 are limited to the administration to lymphoid tissue, claims 29-32 broadly recite the administration of the nucleic acid such that any hematopoietic cells are targeted. These claims read on the administration of the nucleic acid by any route of administration. The applicant argues that articles cited to support the unpredictability of targeting a vector to a particular cell type *in vivo* are not applicable to the instant claims since the specification teaches the direct administration of the vectors to the lymphoid tissue. However, claims 29-32 are not so limited. Furthermore, as discussed in the previous office action, the specification fails to provide guidance as to vectors useful for the instant methods other than plasmid vectors, or provide guidance for the targeted expression either *in vivo* or *ex vivo* of a gene in any hematopoietic cell such that the level of gene expression results in a therapeutic effect on any condition. The cited articles support not only the unpredictability of targeted gene delivery, but the unpredictability of therapeutic gene expression *in vivo* using currently available expression vectors (Eck et al., Verma et al., Deonarian, and Miller et al.). Therefore, in view of the art recognized unpredictability of targeted gene expression *in vivo*, the lack of guidance provided by the specification for vectors suitable for targeting hematopoietic cells *in vivo*, the lack of working examples concerning methods of targeted delivery

other than intrasplenic injection, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The rejection of claims 3-4, 18-19, 29-32, and 34 under 35 U.S.C. 112, second paragraph for indefiniteness of the term "hematopoietic cell expression element" is withdrawn.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32 and 34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the method of claim 29 wherein said hematopoietic stem cell is targeted *ex vivo*. Claim 29 is a method of treating a condition comprising the single step of administering a nucleic acid molecule. It is confusing how a condition in a mammal could be treated if cells are targeted *ex vivo* without being returned to the mammal.

Claim Rejections - 35 USC § 102

The rejections of claims 3-4, 18-19 and 29-32 under 102(a) or 102(b) over Gerloni et al. (1998) are withdrawn in view of applicant's declaration under In re Katz.

The rejections of claims 3-4, 18-19 and 29-32 under 102(a) or 102(b) over Gerloni et al. (1997) are withdrawn in view of applicant's declaration under In re Katz.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Banerji et al. (1983) Cell, Vol. 33, 729-74. The applicant claims nucleic acids comprising a B cell expression element operatively linked to a heterologous polypeptide. Banerji et al. teaches a plasmid encoding the β-globin gene operatively linked to the immunoglobulin enhancer/promoter which is a B cell specific promoter element (Banerji et al., page 730, Figure 1, and page 732, Figure 2). Thus, by teaching all the elements of the claims, Banerji et al. clearly anticipates the instant invention.

Claim Rejections - 35 USC § 103

The rejection of claims 3, 4, and 18-19 under 35 U.S.C. 103 over U.S. Patent 5,508,386 or 5,583,202 in view of Banerji et al. is withdrawn in view of new grounds of rejection of the claims as set forth below.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-4,18-19, and 29-31 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Hurpin et al. (Jan-Feb. 1998) Vaccine, Vol. 16 (2-3), 208-215 in view of in view of Banerji et al. (1983) Cell, Vol. 33, 729-740. The applicant claims nucleic acids comprising a B cell expression element operatively linked to a heterologous polypeptide, and methods of inducing an immune response or treating a condition by administering said nucleic acid to lymphoid tissue.

Hurpin et al. teaches the intrasplenic immunization of mice with a nucleic acid encoding human p53 resulting in the generation of p53 specific CTL and the partial protection of mice from tumor challenge (Hurpin et al., page 208, abstract). Hurpin et al. does not specifically teach the use of a B cell specific promoter. Banerji et al. supplements Hurpin et al. by teaching a plasmid encoding the β-globin gene operatively linked to the immunoglobulin enhancer/promoter which is

a B cell specific promoter element (Banerji et al., page 730, Figure 1, and page 732, Figure 2). Banerji et al. further provides motivation for using a B cell specific promoter by teaching that use of the immunoglobulin heavy chain promoter/enhancer to express a heterologous gene results in two fold increase in the magnitude of β-globin expression (Banerji et al., page 729, abstract). Thus, based on the increased magnitude of gene expression using the immunoglobulin promoter as taught by Banerji et al., and the large percentage of B cells in the spleen, it would have been *prima facie* obvious at the time of filing to substitute the immunoglobulin heavy chain transcriptional elements taught by Banerji et al. for the promoter taught by Hurpin et al. in order to increase antigen expression in the spleen and thus increase resulting immune responses. Based on the successful generation of immune responses observed by Hurpin et al. using intrasplenic injection, and the activity of the immunoglobulin promoter observed by Banerji, the skilled artisan would have had a reasonable expectation of success in using the immunoglobulin heavy chain promoter/enhancer in the vectors and methods taught by Hurpin et al.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 8:30-6:00. General inquiries should be directed

to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER